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# Patient-rated changes in fatigue over a 12-month period predict poor outcome in chronic heart failure

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<b>Aims</b>	Little is known about the factors that are associated with changes in fatigue in chronic heart failure (CHF). Moreover, it is unclear whether these changes have prognostic impact. The aim of this study was to examine these issues.
<b>Methods and results</b>	Three hundred and eighty-seven CHF patients were assessed twice (at baseline and at 12-month follow-up) for exertion and general fatigue. Regression models were developed to assess whether baseline characteristics predicted changes in fatigue and to assess the effect of changes in fatigue on cardiac events occurring beyond 12-months of follow-up. An increase in exertion fatigue over a 12-month period was predicted by higher left ventricular ejection fraction ( $P = 0.02$ ) and cognitive-affective depressive symptoms ( $P = 0.03$ ) at baseline, and not having a biventricular pacemaker shortly after baseline ( $P = 0.02$ ), whereas an increase in general fatigue was only predicted by cognitive-affective depressive symptoms ( $P = 0.002$ ). One hundred and forty-three patients (37%) experienced an event (readmitted, 117; death, 26). An increase in exertion fatigue was associated with a near two-fold increased risk of events beyond 12-months of follow-up (hazard ratio = 1.78; 95% confidence interval 1.18–2.68, $P = 0.006$ ), while controlling for standard cardiac risk factors.
<b>Conclusion</b>	Baseline clinical and psychosocial factors predicted changes in fatigue. Increased exertion fatigue independently predicted an increased risk of cardiac re-admission or death.
<b>Keywords</b>	Fatigue • Chronic heart failure • Re-admission • Prognosis

## Introduction

Fatigue is commonly reported by chronically ill patients.<sup>1–3</sup> In chronic heart failure (CHF), fatigue is one of the most prevalent and distressing symptoms, which is also associated with disease progression.<sup>4–7</sup> Nevertheless, research concerning the clinical relevance of self-reported fatigue in CHF is underreported in the cardiovascular literature, which may partially be due to its ambiguous nature.

Explaining fatigue in CHF has proven to be difficult.<sup>6,8</sup> Previous studies have shown that left ventricular function measures relate poorly to fatigue.<sup>9,10</sup> Fatigue may be due to impaired skeletal muscle blood supply as a result of reduced cardiac output.<sup>11</sup>

Recently, it has been suggested that chronic, low grade haemodynamic stress, as seen in CHF, may lead to dominance of catabolic processes. This in turn leads to skeletal myopathy, causing the sensation of fatigue.<sup>11,12</sup> However, it remains unclear to what extent these factors may fully explain individual differences in fatigue.

Previous studies have demonstrated patients' self-assessment of CHF symptoms to be independently associated with poor prognosis.<sup>13,14</sup> In addition, it has been shown that self-assessed symptoms and New York Heart Association (NYHA) classification are not coherent,<sup>13</sup> indicating that there is little agreement between patient- and physician-rated CHF symptoms. Self-assessed fatigue may therefore provide useful additional information about the patients' clinical and prognostic status.

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The dynamic nature of symptoms, in general, and fatigue, in particular, makes it necessary to examine these symptoms prospectively over time. Efforts should be made to gain knowledge about subgroups of CHF patients who are at increased risk of developing worse fatigue status over time, thereby providing an opportunity for risk stratification and prevention. Moreover, the prognostic impact of changes in self-reported fatigue should be examined as well.

The aims of this study were: (i) to determine clinical, demographic, and psychological predictors of changes in fatigue over a 12-month period and (ii) to examine whether these changes in fatigue were predictive of adverse cardiac events occurring beyond 12 months in patients with systolic CHF.

## Methods

### Patients

Patients attending the heart failure outpatient clinic of the TweeSteden Hospital, Tilburg, the Netherlands, were eligible to participate in the study. Inclusion criteria were defined as systolic heart failure, left ventricular ejection fraction (LVEF)  $\leq 40\%$ , and sufficient understanding of spoken and written Dutch language. Exclusion criteria were defined as diastolic heart failure, age  $\geq 80$  years, myocardial infarction in the month prior to inclusion, and other life-threatening diseases.

Patients completed a questionnaire at baseline and at the 12-month follow-up. Information about cardiac re-admission or death was collected beyond the 12-month follow-up. The overall design of the study is shown in Figure 1. The hospital's medical Ethics Committee approved the study protocol, and the study was carried out according to the Helsinki Declaration. All patients provided written informed consent.

### Changes in fatigue

Previous research has suggested how to differentiate between exertion and general fatigue. The former refers to fatigue directly related to performing of activities in daily living,<sup>15</sup> whereas the latter refers to an overwhelming, sustained sense of exhaustion that does not necessarily have a relationship with exertion.<sup>16</sup> The Dutch Exertion Fatigue Scale (DEFS) assesses exertion fatigue by means of nine items.<sup>15</sup> Items are answered with five response alternatives, ranging from 0 (no) to 4 (yes). Cronbach's alpha was good in the present study ( $\alpha = 0.91$ ). The Fatigue Assessment Scale (FAS) was used to assess general fatigue.<sup>17</sup> This questionnaire consists of 10 items, which are answered on a 5-point Likert scale, ranging from 1 (never) to 5 (always). In the present study, the reliability of this instrument was high ( $\alpha = 0.90$ ).

Changes in exertion and general fatigue were calculated by means of residualized change scores ( $\Delta$ exertion fatigue<sub>res</sub> and  $\Delta$ general fatigue<sub>res</sub>). These changed measures reflect the degree to which an

individual increased or decreased more than would be expected given his or her initial status. Residualized change scores are preferable to simple change scores because they eliminate autocorrelated error and regression to the mean effects.<sup>18</sup>

### Clinical events beyond 12-month follow-up

Patients' hospital medical records were used to assess whether patients had been re-admitted for cardiovascular causes since the 12-month follow-up. The same procedure was followed to assess mortality. Accordingly, the combined clinical endpoint was defined as cardiac hospital re-admission or death. The mean duration of follow-up counting from 12 months after baseline was 782 days (range 1–1798).

### Clinical correlates

Clinical variables included LVEF, NYHA class, aetiology of CHF, cardiac history, biventricular pacemaker status, smoking status, body mass index (BMI), 6 min walking test, physical inactivity, co morbidities, and medication. Information on clinical variables was obtained from the patients' medical records and from the treating cardiologist. Socio-demographic information included sex, age, marital status, and educational level.

### Symptoms of dyspnoea

As dyspnoea is one of the core symptoms of CHF, it was included as a potential predictor of changes in fatigue. Symptoms of dyspnoea were measured by a subscale of the Health Complaint Scale.<sup>19</sup> Items are answered on a 5-point Likert scale, ranging from 0 (not at all) to 4 (extremely).

### Symptoms of depression

Symptoms of depression were assessed by means of the Beck Depression Inventory (BDI).<sup>20</sup> Each item is rated on a 0–3 scale. The BDI is a reliable and well-validated measure of depressive symptomatology<sup>21,22</sup> and is the most widely used self-reported measure of depression. As the somatic items of the BDI may be confounded by fatigue, only the cognitive-affective subscale was used.<sup>23</sup>

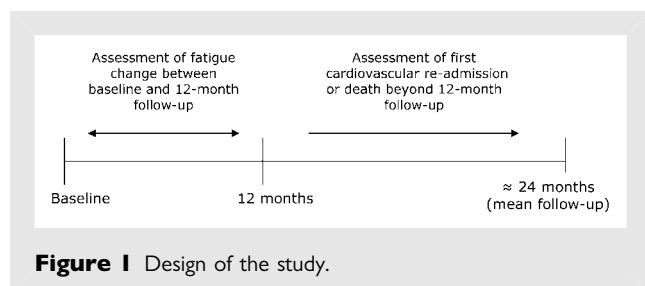
### Type-D personality

Personality was also used as a potential determinant of changes in fatigue. Type D personality was assessed by means of the 14-item type D scale, which comprises two subscales: negative affectivity and social inhibition.<sup>24</sup> A standardized cut-off score  $\geq 10$  on both subscales classifies individuals as having a type D personality. Both scales have good internal reliability ( $\alpha = 0.88$  and  $0.86$ , respectively) and are stable over time.<sup>24,25</sup>

### Statistical analyses

Prior to statistical analyses, educational level, marital status, NYHA class, aetiology of heart failure, co-morbidities, and cardiac history were recoded into dichotomous variables. At 12 months of follow-up, 19.4% of the DEFS scores and 19.1% of the FAS scores were missing. Simply excluding these patients wastes potential information and could bias results. Therefore, SAS procedure multiple imputation was used to create ten data sets to estimate values for missing data. After ordinary analysis, SAS procedure MIANALYZE was used to combine the results of the ten data sets.<sup>26,27</sup>

SAS procedure REG was used to determine predictors of changes in fatigue. All baseline variables were forced into a multivariable model predicting, respectively, changes in exertion fatigue and general fatigue. Cox proportional hazards regression, by means of the SAS procedure PHREG, was used to assess whether changes in fatigue



predicted the combined endpoint of cardiovascular re-admission or death beyond the 12 month follow-up. In multivariable analysis, we included standard cardiac risk factors (age, sex, smoking, BMI, physical inactivity, hypertension, hypercholesterolaemia, and diabetes), measures of disease severity (LVEF and NYHA class), and variables that predicted changes in fatigue.

## Results

### Baseline characteristics

Of the original 419 patients included in the study, 32 were excluded from the final analysis because they died between baseline and 12-month follow-up; hence, changes in fatigue could not be assessed. Patients who completed the study differed systematically from those who died within 12 months after baseline. Patients who died were more likely to be older ( $t = 2.76$ ,  $df = 419$ ;  $P = 0.006$ ), male ( $\chi^2 = 4.31$ ,  $df = 1$ ;  $P = 0.04$ ), physically inactive ( $\chi^2 = 4.06$ ,  $df = 1$ ;  $P = 0.04$ ), and were more likely to be in NYHA class III/IV ( $\chi^2 = 6.02$ ,  $df = 1$ ;  $P = 0.01$ ). In addition, they had lower ejection fraction ( $t = -2.83$ ,  $df = 404$ ;  $P = 0.005$ ) and lower exercise capacity ( $t = -4.11$ ,  $df = 413$ ;  $P < 0.001$ ). Baseline levels of both exertion ( $t = 3.18$ ,  $df = 415$ ;  $P = 0.002$ ) and general fatigue ( $t = 2.14$ ,  $df = 413$ ;  $P = 0.03$ ) were significantly higher in patients who died between baseline and 12 months of follow-up when compared with patients who completed the study. Baseline characteristics of the 387 patients included in the final analysis are displayed in Table 1. The mean age of patients was 66.4 years, 70.3% were male, and 42.9% were in NYHA class III/IV.

### Predictors of changes in fatigue

Multiple regression analysis revealed that changes in exertion fatigue over a 12-month period were predicted by LVEF, implantation of a biventricular pacemaker (BVP), beta-blockers, and cognitive-affective depressive symptoms. Patients having a higher LVEF, having more cognitive-affective depressive symptoms, not having a BVP, and not using beta-blockers were more likely to have an increase in exertion fatigue at the 12-month follow-up. Changes in general fatigue were only predicted by cognitive-affective depressive symptoms. Patients with higher levels of depressive symptoms showed a greater increase in general fatigue at the 12-month follow-up when compared with those with lower levels of depressive symptoms (Table 2).

### Changes in fatigue and hospital re-admission/death

As indicated before, the composite endpoint was defined as cardiac hospital re-admission or death that occurred beyond the 12-month follow-up assessment of fatigue. The mean duration of follow-up counting from 12 months after baseline was 782 days (range 1–1798). Over the period of follow-up, 143 patients (37%) experienced an event (re-admitted, 117 and death, 26).

In univariable analysis, an increase in both general fatigue [hazard ratio (HR) = 1.04, 95% confidence interval (CI) 1.00–1.07;  $P = 0.03$ ] and exertion fatigue (HR = 1.04, 95% CI 1.01–1.07;  $P = 0.005$ ) were associated with an increased risk of cardiovascular re-admission or death. In multivariable analysis, we controlled for

**Table 1** Baseline characteristics ( $n = 387$ )

Age (SD)	66.4 (10.7)
Male, % ( $n$ )	70.3 (272)
Low educational level, % ( $n$ )	33.3 (129)
Having a partner, % ( $n$ )	70.8 (274)
Smoking, % ( $n$ )	23.0 (89)
Body mass index (SD)	28.6 (12.0)
Physical inactivity, % ( $n$ )	44.2 (171)
LVEF (SD)	30.7 (6.8)
NYHA class III/IV, % ( $n$ )	42.9 (166)
Ischaemic aetiology, % ( $n$ )	54.5 (211)
Hypertension, % ( $n$ )	39.8 (154)
Hypercholesterolaemia, % ( $n$ )	47.5 (184)
Diabetes, % ( $n$ )	23.8 (92)
Co-morbidity, % ( $n$ ) <sup>a</sup>	38.0 (147)
Implementation of BVP, % ( $n$ ) <sup>b</sup>	9.3 (36)
Cardiac history, % ( $n$ ) <sup>c</sup>	57.4 (222)
ACE inhibitors, % ( $n$ )	73.1 (283)
Diuretics, % ( $n$ )	72.6 (281)
Beta-blockers, % ( $n$ )	66.9 (259)
Statins, % ( $n$ )	49.9 (193)
Aspirin, % ( $n$ )	42.9 (166)
Psychotropic medication, % ( $n$ )	13.2 (51)
6 min walking test (SD)	276.3 (159.6)
Symptoms of dyspnoea (SD)	2.4 (2.2)
Cognitive-affective depressive symptoms (SD)	1.3 (2.8)
Type-D personality, % ( $n$ )	19.6 (76)

<sup>a</sup>Stroke, chronic obstructive pulmonary disease, peripheral arterial disease, liver disease, and renal insufficiency.

<sup>b</sup>Implementation of a biventricular pacemaker shortly after baseline.

<sup>c</sup>History of MI, CABG, and PCI.

**Table 2** Multivariable predictors of change in fatigue<sup>a</sup>

Variable	$\beta$ -value	P-value
Exertion fatigue		
LVEF	0.13	0.02
Implementation of BVP	−0.14	0.03
Beta-blocker	−0.11	0.05
Cognitive-affective depressive symptoms	0.17	0.02
General fatigue		
Implementation of BVP	−0.12	0.09
Statins	−0.13	0.07
Cognitive-affective depressive symptoms	0.20	0.002

<sup>a</sup>Only variables with  $P < 0.10$  are reported.

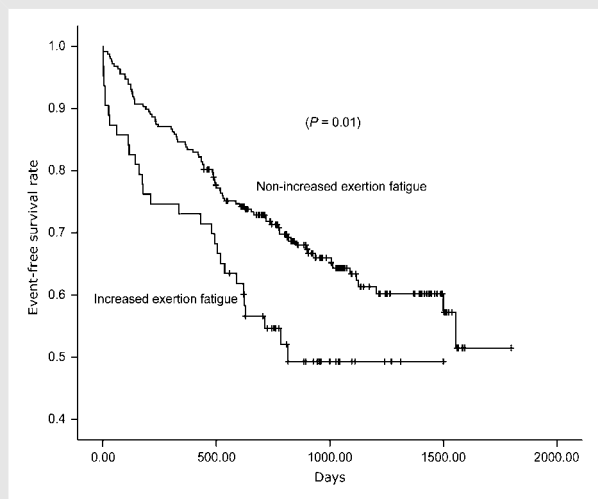
BVP, biventricular pacemaker; LVEF, left ventricular ejection fraction.

the variables listed in Table 3. Accordingly, increased exertion fatigue was an independent predictor of cardiovascular re-admission or death (HR = 1.04, 95% CI 1.00–1.07;  $P = 0.03$ ). Smoking (HR = 1.58, 95% CI 1.08–2.32;  $P = 0.02$ ), BMI (HR = 1.01, 95% CI 1.00–1.02;  $P = 0.04$ ), and diabetes (HR = 1.61, 95% CI

**Table 3** Multivariable predictors of cardiovascular re-admission or death

Variable	HR	95% CI	P-value
Age (SD)	1.00	0.98–1.01	0.72
Male	1.46	0.97–2.21	0.07
Hypertension	0.82	0.58–1.17	0.28
Hypercholesterolaemia	0.99	0.68–1.45	0.97
Smoking	1.58	1.08–2.32	0.02
Body mass index	1.01	1.00–1.02	0.04
Physical inactivity	1.16	0.82–1.65	0.40
Diabetes	1.61	1.09–2.36	0.02
LVEF (SD)	0.99	0.97–1.02	0.49
NYHA class III/IV	1.37	0.95–1.96	0.09
Statins	1.17	0.80–1.73	0.42
Beta-blocker	0.92	0.64–1.33	0.67
Implantation of BVP	0.62	0.30–1.28	0.19
Cognitive-affective depressive symptoms	1.00	0.94–1.06	0.94
$\Delta$ General fatigue <sub>res</sub>	1.01	0.97–1.05	0.59
$\Delta$ Exertion fatigue <sub>res</sub>	1.04	1.00–1.07	0.03

BVP, biventricular pacemaker; LVEF, left ventricular ejection fraction.



**Figure 2** Event-free survival rate of cardiovascular re-admission or death according to increases in exertion fatigue.

1.09–2.36;  $P = 0.02$ ) also predicted cardiovascular re-admission or death. General fatigue did not predict clinical events in the multivariable analysis (Table 3).

Next,  $\Delta$ exertion fatigue<sub>res</sub> was dichotomized using the highest quintile ( $\Delta$ exertion fatigue<sub>res</sub>  $< 5 = 0$  and  $\Delta$ exertion fatigue<sub>res</sub>  $\geq 5 = 1$ ). Accordingly, the event rate was 34% ( $n = 104$ ) in the non-increased exertion fatigue group and 46% ( $n = 39$ ) in the increased exertion fatigue group. The Kaplan–Meier curve in Figure 2 shows that patients in the increased exertion fatigue group were more likely to experience an event when compared with those in the non-increased exertion fatigue group ( $P = 0.01$ ). Multivariable analysis

revealed that patients in the increased exertion fatigue group had a near two-fold increased risk of experiencing an adverse event (HR = 1.78, 95% CI 1.18–2.68;  $P = 0.006$ ).

## Discussion

To the best of our knowledge, this is the first study to examine the predictors of changes in fatigue over time in CHF patients and to examine the prognostic impact of these changes in fatigue. An increase in exertion fatigue over a 12-month period was predicted by higher LVEF and cognitive-affective depressive symptoms at baseline, and by not having a BVP implanted shortly after baseline. An increase in general fatigue was only predicted by cognitive-affective depressive symptoms.

Increased exertion fatigue at 12 months of follow-up was independently associated with an increased risk of cardiovascular re-admission or death beyond the 12-month follow-up, whereas an increase in general fatigue was only associated with adverse outcomes in the univariable analysis. These results are in line with the studies, which show that fatigue in CHF<sup>7,13,14</sup> and increased fatigue in coronary patients<sup>28</sup> are associated with adverse outcomes.

Fatigue is considered to be one of the most important factors affecting patients quality of life, and there is a growing need for adequate clinical management of fatigue.<sup>29,30</sup> However, little is known about why patients experience fatigue,<sup>31</sup> and explaining individual differences in fatigue has proven to be difficult.<sup>6</sup> The current study identified factors that contribute to change in fatigue over time in CHF patients. In accordance with the previous work,<sup>32</sup> implantation of a BVP was associated with a decrease in exertion fatigue. Changes in both exertion and general fatigue were predicted by cognitive-affective depressive symptoms at baseline. This result extends our previous findings<sup>8</sup> and lends further support to the possible role of depression in the perception and reporting of disease-specific symptoms in CHF.<sup>8</sup> The association between higher LVEF and increased exertion fatigue was counter-intuitive, but it could be that better status on both LVEF and exertion fatigue at baseline is more likely to deteriorate than if either or both are already significantly impaired.

The current study emphasizes the importance of recognizing changes in fatigue in clinical practice. Recognition of these changes allows healthcare professionals to act on this, for example, by offering exercise training. The importance of exercise training was recently reviewed in a meta-analysis by Puetz *et al.*,<sup>33</sup> in which they showed that cardiac rehabilitation exercise programmes have considerable effects on levels of energy and fatigue. However, it remains unclear whether improvement after therapy is associated with improved prognosis. Future studies should address this issue.

In addition, the mechanisms through which fatigue exerts its negative effects are unclear. We hypothesize that mechanisms are different for exertion and general fatigue. Exertion fatigue may primarily reflect the direct physical consequences of the disease itself, and an increase in exertion fatigue may therefore reflect worsening of CHF. Future studies should assess physiological measures that are known to be abnormal in CHF patients and that are relevant with respect to fatigue, for example, measures of abnormal muscle metabolism and an enhanced ergo

reflex response.<sup>11,12</sup> Future studies should measure changes in exertion fatigue and these physiological parameters in parallel. In contrast, general fatigue may reflect more psychological consequences of CHF and may, to some extent, be on a par with mental fatigue. A hint towards this association was given by the fact that the increase in general fatigue was predicted only by cognitive-affective depressive symptoms. Increased general fatigue may therefore have an impact on the patients' ability for self-care, which has been associated with poor prognosis in CHF.<sup>34</sup>

There is also some evidence that vital exhaustion, a concept related to general fatigue, is associated with increased levels of inflammatory markers in patients with coronary heart disease.<sup>35,36</sup> These cytokines have been associated with adverse outcomes in CHF.<sup>37–39</sup> Indeed, one important sign of peripheral inflammatory signals is fatigue and behavioural withdrawal,<sup>40</sup> as part of the sickness response. Further research into the mechanisms responsible for the link between fatigue and CHF prognosis is warranted in order to optimize treatment strategies. Given the failure of anti-tumour necrosis factor medication to improve prognosis in CHF<sup>41</sup> and if increases in fatigue are found to be related to proinflammatory cytokines, such interventions may be more effective if provided specifically to patients with worse fatigue.

This study had a number of limitations. First, there may have been a bias in the selection of patients. The cardiologist or heart failure nurses asked patients to participate in the study, and this interaction pattern might have influenced selection. Secondly, we used combined endpoints in order to increase the number of clinical events and did not use mortality as a separate endpoint. Factors predicting re-admission may differ from those predicting death. Thirdly, we did not have data available on changes in variables other than fatigue. For future studies, it would be interesting to determine whether changes in cardiac function, renal function, 6 min walk test, or peak oxygen consumption are related to changes in fatigue. Fourth, we did not have information on diagnosis of major depression. Nevertheless, the strengths of the current study were the repeated assessment of fatigue over time and the prospective design examining the impact of these changes in fatigue on prognosis. Finally, we used reliable and valid measures of both exertion and general fatigue.

In summary, changes in fatigue were related to clinical and psychosocial factors, and increased exertion fatigue independently predicted an increased risk of cardiac re-admission or death. The current study contributes to the understanding of fatigue in CHF and reveals that changes in fatigue are of clinical and prognostic importance. Taking symptom changes into account, in addition to their biomedical and psychosocial predictors, may lead to improved risk stratification and clinical management in this high-risk patient group.

**Conflict of interest:** none declared.

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